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TITLE: Central Visual Prosthesis With Interface at the Lateral Geniculate Nucleus

PRINCIPAL INVESTIGATOR: Joseph F. Rizzo, MD

CONTRACTING ORGANIZATION: Massachusetts Eye and Ear Infirmary, Neuro-Ophthalmology, Charles Street, Boston, MA 02114

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14. ABSTRACT

The goals of this project are to:
- *Modify microfabrication methods to produce 256 channel, implantable electrode arrays for the Lateral Geniculate Nucleus (LGN)*
- *Adapt visual neuroprosthesis RF coil and titanium package to fit in small hole in skull; update external controller software*
- *Develop surgical insertion tool to deliver the electrodes to LGN*
- *In vitro bench testing of electrode arrays and insertion tools*
- *In vivo implantation and psychophysical testing in non-human primate animal model*

In this reporting period (Year 1), the accomplishments have included:

15. SUBJECT TERMS
Visual Prosthesis; Lateral Geniculate Nucleus

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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Unclassified	Unclassified	Unclassified	Unclassified	11	19b. TELEPHONE NUMBER *(include area code)* (617) 573-3742

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1 **INTRODUCTION:**

The scope of this award concerns the adaptation of a high density implantable neurostimulation system for a visual prosthesis, for the application of providing visual input to the brain's Lateral Geniculate Nucleus (LGN). This device has originally been developed by the PI and his colleagues for application in a sub-retinal visual prosthesis. A thalamic interface for visual input could have far reaching implications, since it would be usable to treat patients with blast induced eye trauma, glaucoma, or diabetic retinopathy who would otherwise not be able to benefit from a prosthesis that introduces artificial vision by interfacing with the retina. To achieve an LGN device, the electrodes need to be adapted to be insertable in the LGN by means of a specialized surgical implantation tool.

2 **KEYWORDS:**

Visual Prosthesis; Lateral Geniculate Nucleus

3 **ACCOMPLISHMENTS:** .

- **What were the major goals of the project?**

The goals of this project are to:
• *Modify microfabrication methods to produce 256 channel, LGN-implantable electrode arrays*
• *Adapt visual neuroprosthesis RF coil and titanium package to fit in small hole in skull; update external controller software*
• *Develop surgical insertion tool to deliver the electrodes to LGN*
• *In vitro bench testing of electrode arrays and insertion tools*
• *In vivo implantation and psychophysical testing in non-human primate animal model*
The first milestone at month 4 was the selection of a process for microfabricating the LGN electrodes; this has been selected (100% complete)

- **What was accomplished under these goals?**

Major Activities / Specific Objectives for this Year:
-Mask design and initial microfabrication of ultra-microelectrode (UME) arrays made from Silicon Carbide and Polyimide at the Cornell NanoScale Facility and the University of Texas, Dallas
-Optimization of surgical insertion tool design for LGN arrays that are compatible with SiC UMEs and the Bionic Eye 256-channel implantable neurostimulator platform
-Refinement of SiC UME design based on initial findings
-Fabrication of complete surgical insertion systems comprised of optimized SiC LGN electrodes and micro-fabricated 'ribbon cables in surgical delivery/insertion devices
-In vitro testing of insertion of SiC UMEs in gel models of brain tissue
-3D model development of the entire peri-operative surgical scheme for device implantation in non-human primate models, and the post-operative device structure, adapting the designs of sub-awardee Bionic Eye's high density neurostimulator

Significant Results:
-Fabrication and testing of LGN electrode arrays, refinement of their design and that of the surgical insertion tools, and insertion of arrays into gel models of brain tissue

Narrative Description:

In the past year, we have refined our electrode array design and fabrication process through several iterations, and have arrived at finalized prototype design that was fabricated and tested in agarose gel models of brain tissue. Initially, we made an initial mock implant by creating a device with electrode 'tines' and a ribbon cable design. This device used a uniform, thin film silicon carbide thickness over the entire length of the device. The silicon carbide (SiC) is both a structural element as well as an electrical insulator that wraps around the microfabricated leads and protects them from ingress of body fluids. The single-SiC fabrication process allowed the lead wires that exit the skull and the electrodes themselves to be fabricated together in a single step.

As the project progressed, we realized that using the required thickness of SiC 'tines' across the entire length of the ribbon cable that leads to the electrodes, resulted in a cable too thick to fit within the confines of the surgical insertion tool that our neurosurgeon at MGH would need to use. In our insertion tool development, we sought to mimic as closely as possible the cannula size currently used in the field to implant Deep Brain Stimulation electrodes.

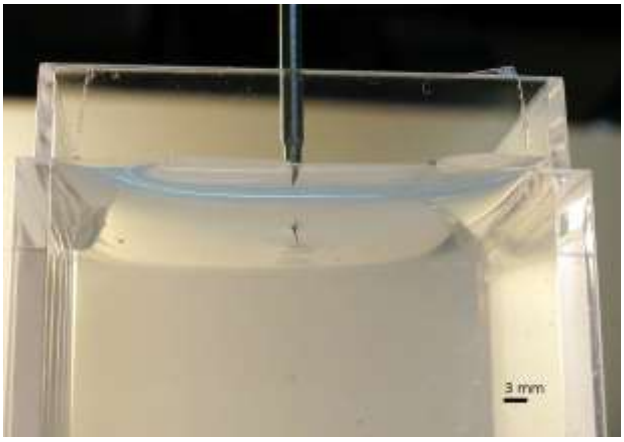
We thus limited ourselves to using a '4 French' size split sheath inserter for our device. We designed in 3D CAD a version that separated the needed 'ribbon cable' and 'electrode tine' functions into two separate pieces that were then individually fabricated.and then bonded together. This allowed the ribbon cable and electrode tines to have different thicknesses, and both fit together within the insertion tool; the split-sheath inserter has a maximum outside diameter of 1.9mm. The bonding of two separately fabricated elements in the electrode array required careful design of the bonding process, and the pads that allow the two components to be aligned and then joined. The bond pads were arranged into a configuration 4x16 bonding sites for our initial 64-channel arrays. Within these bonding pad arrays, micro-separations between sub-arrays formed from flexible polyimide were introduced to reduce the overall stiffness of the parts. This allowed the array to be affixed to the insertion tool without undue stress. We also tried variations of the 4x16 designs, which are shown in the Figures below.

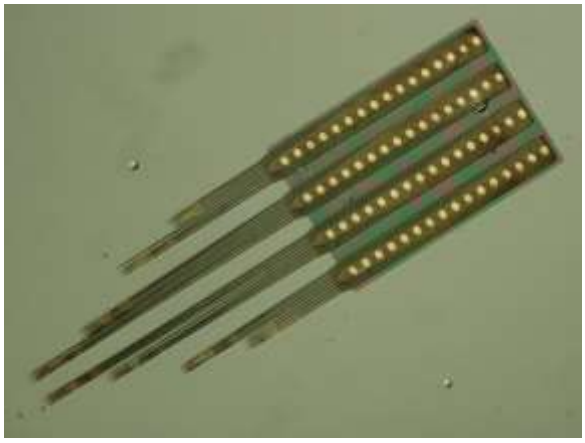
We explored the influence of uniform spacing of the individual electrode tines versus formed groupings of tines, on the ease of insertion of the resulting devices into brain tissue models. Thus, variations we fabricated included one with a uniform distance of 10 μm between each tine on the one hand, and groupings of 8 tines in close proximity on the other hand. Sub-awardee Bionic Eye's collaborator at the University of Texas, Dallas then fabricated these redesigned devices using an established ultra microelectrode fabrication process that was developed in the opening months of this program.

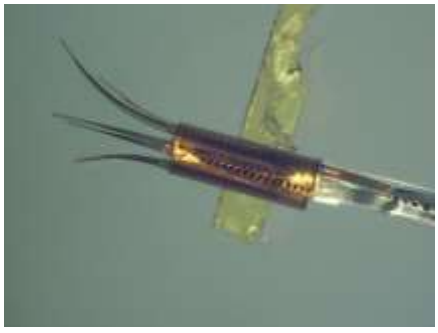
At this time, several approaches for realizing the complete system have been evaluated. Initially, a very simple mechanical mockup device was fabricated in order to evaluate mechanical fit and deal with the overall size limitations given the recommendations of our team's neurosurgeon concerning the maximum bore size of the surgical insertion tool. We then developed means for holding the neurostimulator and radio frequency coil modules that must be affixed to the skull after electrode array insertion; complete 3D models of the peri-operative surgical environment and the post-operative system configuration have been co-developed with sub-awardee Dr. John Pezaris of Massachusetts General Hospital. Since our device must extend from the surface of the brain to the lateral geniculate nucleus (LGN), it is being developed as an assembly of 2 components. These include the microfabricated ribbon cable that extends from the neurostimulator package to just before the active electrode array, and a number of different possible electrode array designs. The two microfabrication processes do not lend themselves to integration into a single step, due to the competing requirements for the two parts – that is, flexibility for the ribbon cable, and stiffness for the penetrating electrode array shafts. As stated above, we have now developed the ability to fabricate both types of parts and integrate them into a complete implantable system, which we then evaluated in gel models of tissue. We also evaluated alternative bonding techniques, including 'tab' bonding and stud or rivet bonding, to join the two portions of the electrode arrays to one another.

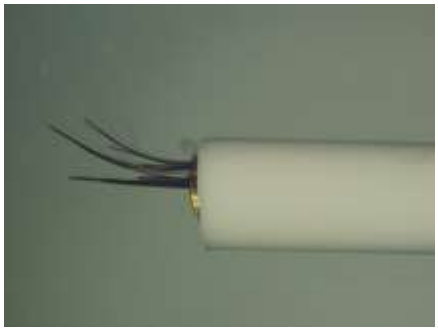
A patent application is being prepared for the overall design. 3D modeling was performed using SolidWorks software to generate the images below, which depict how the electrode array is attached to the inserter and how the inserter carefully protects the delicate electrode tines before and during insertion into brain tissue. We procured custom fabricated parts, and off-the-shelf tubing, metal push rods and split inserter sheaths from industrial vendors.

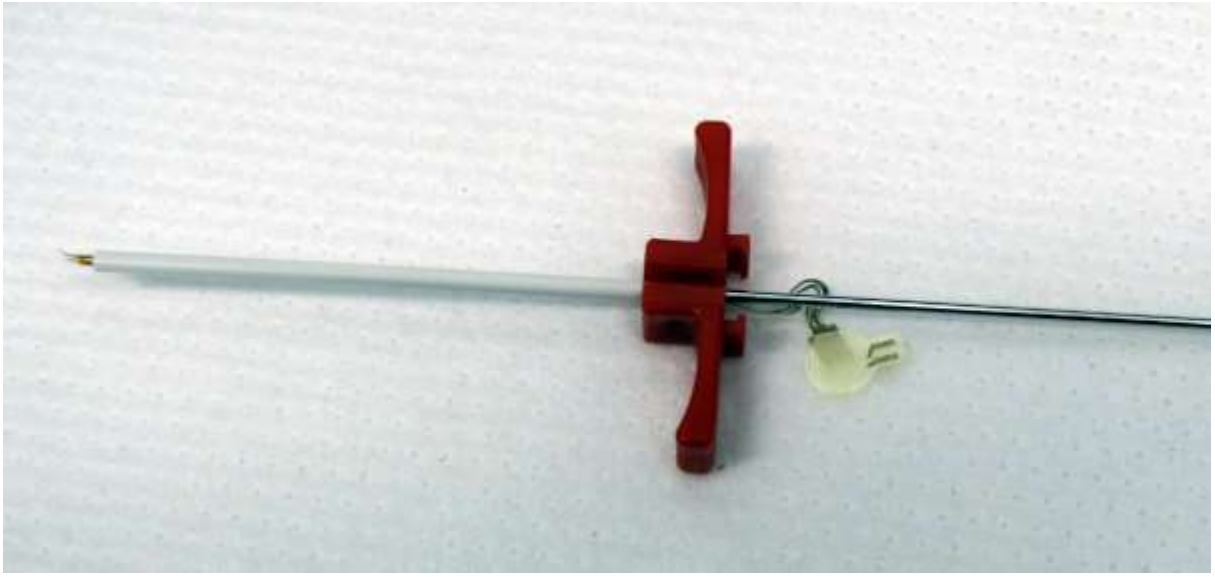
In the balance of CY17, sub-awardee Bionic Eye will complete fabrication and testing of active LGN neurostimulator systems according to our designs, and these will be delivered to our other sub-awardee Dr. Pezaris at MGH for implantation in non-human primate animal models. The progression of our system development to date can be seen in the Figures below.



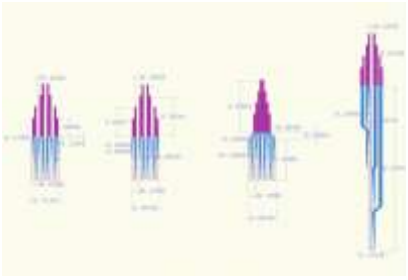


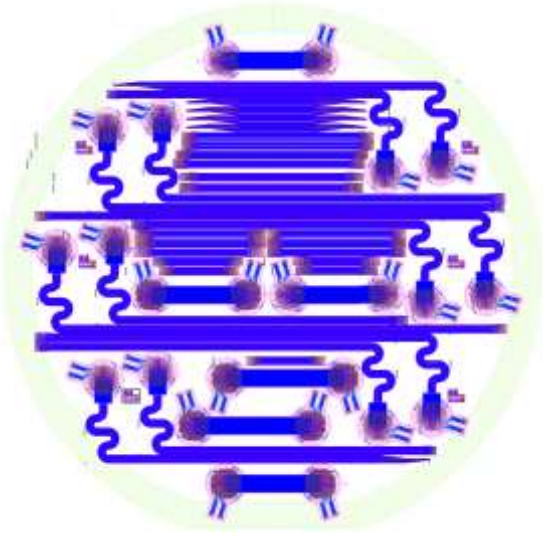


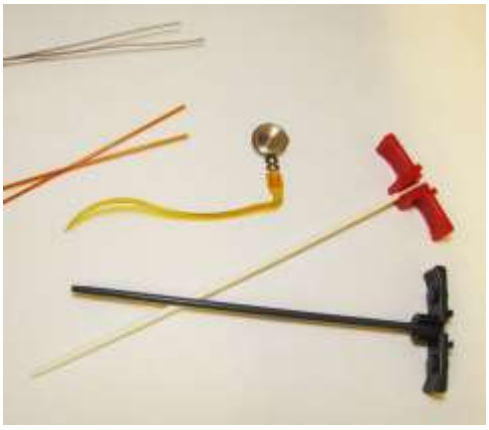


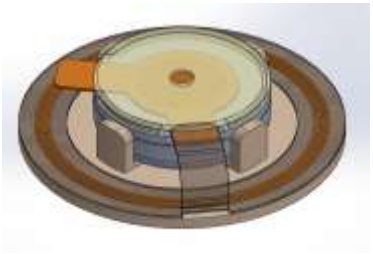


Annual Report figures on this page, top to bottom: Insertion of SiC ultra microelectrodes (UMEs) into gel model of brain tissue by Dr. Pezaris' lab at MGH; Micro-fabricated UME array with bonding pads on Si wafer; UME array bonded to microfabricated ribbon cable and loaded into custom surgical insertion tool; complete system loaded in split sheath inserter ready for in vitro insertion test.









Annual Report figures on this page, clockwise from upper left:

CAD drawings of penetrating SiC electrodes for the LGN, and a ribbon cable to connect the electrodes to the signal feedthroughs on sub-awardee Bionic Eye Technologies' high density implantable neurostimulator; mock electrode array and split sheath surgical inserters prior to assembly; 3D models showing assembly sequence for mounting the penetrating electrode array on the surgical insertion and loading it into the split-sheath device; scaffold holding the round titanium micro-package for the visual prosthesis and the RF coil that receives power and data from the external controller; split sheath inserter mounted on a micro-drive motor; and, a CAD drawing showing the layout of the ribbon cable arrays on a 4 inch silicon wafer.

- **What opportunities for training and professional development has the project provided?**

Nothing to report; however, PI Dr. Rizzo and sub-award PI Dr. Pezaris of Massachusetts General Hospital will present on this project at The Eye And The Chip 2017 Conference in Detroit, MI in September, 2017.

- **How were the results disseminated to communities of interest?**

Nothing to report

- **What do you plan to do during the next reporting period to accomplish the goals?**

Bionic Eye's sub-award PI, Dr. Doug Shire, and microfabrication engineer Dr. Marcus Gingerich will assemble bonded, hybrid SiC/polyimide electrode arrays for this study with Dr. Cogan and his team at UT Dallas, and sub-awardee Dr. John Pezaris of Massachusetts General Hospital (MGH). These arrays will be attached to complete high-density neurostimulator systems by Bionic Eye and delivered to sub-awardee Dr. Pezaris at MGH for implantation in a non-human primate animal model in CY17. Dr. Pezaris is also advising our team on the custom surgical insertion tool for the device, and has participated in weekly team conference calls that PI Rizzo attends. These tasks are in service of the second major milestone, which is the completion of the implantable neurostimulator units and associated insertion tools.

In the coming quarter, electrically-active penetrating electrode arrays for the LGN will be fabricated and will be assembled to custom ribbon cable assemblies and loaded into surgical insertion tools to implant the arrays. The arrays will be paired with Bionic Eye titanium neurostimulator modules. The resulting devices will first be inserted in gel models of the brain to ensure that the final parts delivered to Dr. Pezaris at MGH will be compatible with neurosurgery equipment there, and ready to implant in non-human primates near the end of the CY17 period.

4 **IMPACT:**

- **What was the impact on the development of the principal discipline(s) of the project?**

If successful, a viable LGN based visual prosthesis would not only provide useful vision restoration for millions of potential patients who would otherwise not benefit from a retinal prosthesis.

- **What was the impact on other disciplines?**

The LGN surgical insertion tool and electrode assembly may readily be adapted to other advanced neuromodulation systems, such as improved deep brain stimulation devices.

- **What was the impact on technology transfer?**

A patent application on the LGN surgical insertion tool and electrode assembly is being prepared for submission; this will be co-authored by the PI and the sub-award PIs, and will be further developed by startup company Bionic Eye Technologies, Inc.

- **What was the impact on society beyond science and technology?**

Nothing to report

5 **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

Nothing to report

- **Actual or anticipated problems or delays and actions or plans to resolve them**

  Nothing to report

- **Changes that had a significant impact on expenditures**

  There was an initial delay in establishing the two major sub-awards under this program to Massachusetts General Hospital and to Bionic Eye Technologies, Inc. that will result in a request to carry some Year 1 funds over into Year 2. Nevertheless, good progress has been made toward the project milestones, which is outlined above.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

  - **Significant changes in use or care of human subjects**

  Nothing to report

  - **Significant changes in use or care of vertebrate animals.**

  Nothing to report; an IACUC protocol for the non-human primate study has been submitted by sub-award PI Dr. Pezaris at Massachusetts General Hospital.

  - **Significant changes in use of biohazards and/or select agents**

  Nothing to report

6 **PRODUCTS:**

- **Publications, conference papers, and presentations**

  - **Journal publications.**

  Nothing to report

  - **Books or other non-periodical, one-time publications.**

  Nothing to report

  - **Other publications, conference papers, and presentations.**

  Abstracts have been accepted for presentations by PI Rizzo and sub-award PI Pezaris on the topic of this work at the Eye And The Chip conference in Detroit, MI in September, 2017.

- **Website(s) or other Internet site(s)**

  Nothing to report

- **Technologies or techniques**

  Nothing to report

- **Inventions, patent applications, and/or licenses**

  A patent application is being prepared by PI Rizzo and sub-award partners Dr. Pezaris at MGH and Dr. Shire at Bionic Eye on the LGN surgical insertion tool and associated electrode technology. It will be submitted in July 2017.

- **Other Products**

  Nothing to report

7 **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

- **What individuals have worked on the project?**

Name: Dr. Joseph Rizzo, MD
Project Role: Principal Investigator, Massachusetts Eye and Ear Infirmary
Researcher Identifier: N/A
Nearest person month worked: 2
Contribution to Project: Coordinating, negotiatiating, and supervision of two major sub-awards to Massachusetts General Hospital and to Bionic Eye Technologies, Inc.

Name: Dr. Douglas Shire, Ph.D.
Project Role: PI on Sub-Award to Bionic Eye Technologies, Inc.
Researcher Identifier: N/A
Nearest person month worked: 3
Contribution to Project: Coordinating of vendors, collaborators and Bionic Eye staff for the production, testing and programming of implantable high-density LGN stimulators for delivery to sub-awardee Massachusetts General Hospital for non-human primate studies

Name: Dr. Marcus Gingerich, Ph.D.
Project Role: Microfabrication Engineer under Sub-Award to Bionic Eye Technologies, Inc.
Researcher Identifier: N/A
Nearest person month worked: 3
Contribution to Project: Dr. Gingerich is responsible for the micro-fabrication of ultra-microelectrode arrays for use in the LGN and the interfacing of such arrays to the HD Bionic Eye implantable neurostimulator

Name: Dr. John Pezaris, Ph.D.
Project Role: PI on Sub-Award to Massachusetts General Hospital
Researcher Identifier: N/A
Nearest person month worked: 2
Contribution to Project: Submission and execution of non-human primate animal surgical protocols for implantation and testing of the HD LGN neurostimulator components provided by sub-awardee Bionic Eye Technologies, Inc.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to Report

- **What other organizations were involved as partners?**

Nothing to Report

8 **SPECIAL REPORTING REQUIREMENTS**

- **COLLABORATIVE AWARDS:** N/A
- **QUAD CHARTS:** The most recent Quad Chart for this project is attached as an Appendix.

APPENDICES:.1. Quad Chart covering the period 4/1/2017 – 6/30/2017

Central Visual Prosthesis with Interface at the Lateral Geniculate Nucleus

Award W81XWH-16-2-0015

Vision Research Program: Pilot Technology Development

PI: Joseph F. Rizzo, MD **Org: Massachusetts Eye and Ear Infirmary** **Award Amount: $309,147**

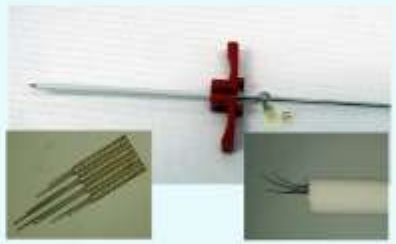
Study/Product Aim(s)

- Modify microfabrication methods to produce 256 channel, deep brain implantable electrode arrays
- Adapt visual neuroprosthesis RF coil and titanium package to fit in small hole in skull; update external controller software
- Develop surgical insertion tool to deliver the electrodes to LGN
- In vitro bench testing of electrode arrays and insertion tools
- In vivo implantation and psychophysical testing in non-human primate animal model

Approach

The purpose of this proposal is to adapt a record high density 256 channel retinal neurostimulation system previously developed by the PI and his colleagues, to a new visual prosthesis that will interface with the brain at the lateral geniculate nucleus, and to validate the design by implanting and testing the device.

Insertion of SiC Ultra-Microelectrode Array into Gel Model of Brain Tissue



Split-sheath Surgical Insertion Tool Loaded with Ultre Microelectrode (UME) Array. Insets: UME on Si Wafer & Insertion Tool Tip Close-Up

Figures: PI Rizzo, Bionic Eye and collaborator University of Texas, Dallas have assembled silicon carbide ultra-microelectrode arrays (UMEs) and surgical insertion tools capable of implanting completed devices in the LGN

Timeline and Cost

Activities CY	15	16	17	18
Electrode Array Fabrication				
Develop Surgical Insertion Tool				
In Vitro Bench Testing of Devices				
In Vivo Implantation and Testing in Monkey Animal Model				
Estimated Budget ($K)		**$150**	**$100**	**$60**

Updated: 6/30/2017

Goals

CY16 Goals – Hardware Adaptation, Surgical Tools
☐Develop Initial Fabrication Methods for HD LGN Electrode Arrays
☐Initial Design of Surgical Insertion Tool for LGN Electrode Arrays
CY17 Goals – In Vitro Tests; Software Updates; Begin Animal Trial
☐Validate Design of Electrode Arrays & Surgical Tools in Gel models of Brain Tissue, Perform Bench-top Testing, and Implant First Animal
☐Update External Controller Software Code for LGN Application
CY18 Goal – Complete Animal Study at MGH under Sub-Award
☐ Perform biocompatibility and psychophysical testing

Comments

- LGN SiC ultra-microelectrode array designs have been fabricated and tested in gel models of brain tissue in Q4 by sub-awardees Bionic Eye and MGH. A patent is being applied for on the surgical tool design. Complete system implantation will follow in CY17.